PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

To:

Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

Date of mailing *(day/month/year)*	10.08.2001
Applicant's or agent's file reference 14228-1pct CC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00515	04/05/2000	05/05/1999

Applicant
NEUROCHEM,INC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Cardenas, C Tel.+31 70 340-3370

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
14228-1pct		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00515	04/05/2000	05/05/1999
Applicant		
NEUROCHEM, INC		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[X] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIO SEARCH REPORT

International application No.
PCT/CA 00/00515

Box I Observations where c rtain claims wer found unsearchable (Continuati n of item 1 of first sh t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18,19,23-25 and 30 are directed to a method of treatment of the human/animal body or to a diagnostic method practised on the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-6,9-36(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,9-36(partially)

Present claims 1 and 29 relate to peptides or isomers thereof lacking any constant structural domain and almost any definition of the constituting amino acid residues (due to the facultative presence of all constituting Xaa's in formula I and the absence of any structural definition in claim 29), which peptides are defined by reference to desirable characteristics or properties, namely that they inhibit amyloidosis and/or are cytoprotective. Due to the facultative presence of all constituting Xaa's in formula I
The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined in the claims 7 and 8 and their conjugates as defined in claim 9, their compositions and use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 8(complete),1-7,9-36(partially)

   Compounds having the structure defined in claim 7, SEQ ID NO: 1-20,23 and 24,their compositions and use

2. Claims: 1-7,9-36(partially)

   Compounds having the structure defined in claim 7, SEQ ID NO:21 and 22, their compositions and use

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/CA 00/00515

A. CLASSIFICATION OF SUBJECT MATT[redacted]
IPC 7 C07K14/47 A61K38/17 G01N33/68 A61P25/28 C12N5/00
A61K51/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K G01N C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, PAJ, BIOSIS, MEDLINE, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 08868 A (PRAECIS PHARM INC) 5 March 1998 (1998-03-05) the whole document ---	1-7,9-36
Y	TJERNBERG L O ET AL: "CONTROLLING AMYLOID BETA-PEPTIDE FIBRIL FORMATION WITH PROTEASE-STABLE LIGANDS" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 272, no. 19, 9 May 1997 (1997-05-09), pages 12601-12605, XP002050230 ISSN: 0021-9258 cited in the application See especially Fig.3 --- -/--	1-7,9-36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2000	29. 12. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 28471 A (PHARM PEPTIDES INC) 19 September 1996 (1996-09-19) the whole document	1-7,9-36
A	GIULIAN E.A.: "The HHQK domain of beta-amyloid provides a structural basis for the immunopathology of Alzheimer disease" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 45, 6 November 1998 (1998-11-06), pages 29719-29726, XP002146049 MD US cited in the application the whole document	1-7,9-36
A	WO 97 21728 A (KAROLINSKA INNOVATIONS AB ;NORDSTEDT CHRISTER (SE); NAESLUND JAN () 19 June 1997 (1997-06-19) the whole document	
A	DATABASE WPI Section Ch, Week 199837 Derwent Publications Ltd., London, GB; Class B04, AN 1998-433888 XP002154640 -& JP 10 182695 A (TEIKOKU SEIYAKU KK), 7 July 1998 (1998-07-07) page 6	1-7, 18-21, 23,24, 26,27, 29-32
A	KOERNYEI J ET AL: "TC-99M LABELLING AND BIODISTRIBUTION OF DESIGNED MOLECULES" RADIOACTIVE ISOTOPES IN CLINICAL MEDICINE AND RESEARCH,BIRKHAEUSER VERLAG, BASEL,CH, 1995, pages 287-292, XP000965479 see especially table 2	1-7,9, 11-15, 17,22, 25,28,33
A	TORNEIRO E.A.: "Sequence-elective binding of pepides in water by a synthetic receptor molecule" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 117, no. 21, 1995, pages 5887-5888, XP002154639 DC US see especially Table 1	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/CA 00/00515

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9808868	A	05-03-1998	AU	4238797 A	19-03-1998
			EP	0929574 A	21-07-1999
			US	5985242 A	16-11-1999
WO 9628471	A	19-09-1996	US	5817626 A	06-10-1998
			US	5854215 A	29-12-1998
			AU	5252496 A	02-10-1996
			CA	2214247 A	19-09-1996
			EP	0815134 A	07-01-1998
			JP	11514333 T	07-12-1999
			US	5854204 A	29-12-1998
			US	5985242 A	16-11-1999
WO 9721728	A	19-06-1997	AU	1072897 A	03-07-1997
			EP	0866805 A	30-09-1998
JP 10182695	A	07-07-1998	NONE		

PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14228-1pct		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00515	04/05/2000	05/05/1999
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant NEUROCHEM,INC		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/12/2000	10.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00515

I. Basis of the report

1. With regard to the **lements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,2,4-23	as originally filed			
3,3a	as received on	19/06/2001	with letter of	15/06/2001

Claims, No.:

1-36	as received on	19/06/2001	with letter of	15/06/2001

Drawings, sheets:

1/7-7/7	as originally filed

Sequence listing part of the description, pages:

1/7-7/7, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.
   ☒ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-6,9-36(all partially);18,19,23-25,30 with respect to idustrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 18,19,23-25,30 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-6,9-36(all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	8
	No:	Claims	1-7,9-36
Industrial applicability (IA)	Yes:	Claims	1-17,20-22,26-29,31-36
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re It m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1)Original claims 1 and 29 related to peptides or isomers thereof lacking any constant structural domain and almost any definition of the constituting amino acid residues (due to the facultative presence of all constituting Xaa's in formula I and the absence of any structural definition in claim 29), which peptides are defined by reference to desirable characteristics or properties, namely that they inhibit amyloidosis and/or are cytoprotective.
The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope has been considered to be impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case has been considered to be such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search had been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined in the claims 7 and 8 and their conjugates as defined in claim 9, their compositions and use.
In this respect the examiner refers to Rule 70.2(d) PCT: subject-matter for which no international search report has been established will not be the subject of international preliminary examination.

2)Claims 18,19,23-25,30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

1)In view of the objections made under the Articles 5 and 6 PCT the subject-matter to be examined consists of the compounds of claim 7, their conjugates, their compositions and use.
These compounds are characterized by their ability to inhibit amyloidosis and/or their cytoprotective activity in this respect and therefore each of them can be considered to represent a solution for the problem of preventing amyloidosis.
2)These solutions might, a priori, be considered as satisfying the requirements of unity whereby the feature that the compounds prevent amyloidosis forms the contribution each solution makes over the prior art and therefore provides the special technical feature linking these different solutions.
3)The closest prior art with regard to this subject-matter of the present application is considered to be:

D1:Journal Biol.Chem., Vol.272, No.19, 1997, 12601-12605

This document discloses inhibitors of amyloid-beta-peptide fibril formation with protease-stable ligands, which ligands consist of all-D pentapeptides.
4)In the light of this document it is considered that a common technical link based on the feature that the compounds prevent amyloidosis which could be the unifying concept is no longer present.
5)In the light of D1 the problem to be solved may be considered to be the provision of alternative inhibitors of amyloidosis.
6)Therefore further unified solutions should relate to groups of compounds sharing a common structural element which may be regarded as the special technical feature providing unity; this special technical feature should be an essential structural part common to all of the embodiments of the claimed invention (and responsible for the inventive effect), and which is absent from any solution to the same problem disclosed in the prior art.
7)Regarding all of the proposed solutions as a whole, as defined in independent claim 7, the only common structural features which can be detected are, that the peptides should contain at least one Lys and at least one amino acid residue should be in the D-form. No other common invariant features can be identified as being present in said compounds.
8)It is considered that D1 (see especially Fig.3) discloses peptides which possess the same structural features as those described above (D-aa residues and at least a Lys

residue) and are intended for the solution of the same problem as that underlying the present application. For these reasons it is considered that the compounds claimed in the present claim 7 lack any common structural feature which could be regarded as the special technical feature providing unity to this subject-matter.
9)As no other technical features can be distinguished which, in the light of the prior art, could be regarded as special technical features on which an unifying concept could be based, there is no single inventive concept underlying the plurality of claimed inventions of the present application (see Rule 13.1 PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:J.Biol.Chem., Vol.272, No.19, 1997, 12601-12605
D2:WO-A-9808868

I.Novelty

In view of the available prior art the claims 1-36 are considered to be novel under Art.33(2) PCT: D1 discloses all-D pentapeptides having a Lys residue, however the present peptides have not been specifically disclosed.

II.INVENTIVE STEP

1)The closest prior art is considered to be D2, disclosing peptides originating from the β-sheet domain of amyloid β-peptide having an all-D-aa structure and their use in preventing or detecting amyloidosis (e.g., see claims 1,9-17 and Tables). The choice of D-aa residues is based on the enzymatic resistance they provide to peptides containing them.
2)The present compounds having the SEQ ID NOS 1-20,23 and 24 differ from said prior art compounds essentially only in the presence of Lys which is present in position 16 of the β-sheet domain. Their activity also consists of inhibiting amyloidosis.
3)The problem to be solved may therefore be considered to be the provision of alternative inhibitors of amyloidosis having enzymatic resistance.

4)In the prior art peptides originating from the β-sheet domain of amyloid β-peptide having also the Lys residue in position 16 and exhibiting amyloidosis inhibiting activity were already well-known, as can be exemplified by D1 (see Fig.1).
In the opinion of the examiner it is considered to be within the normal skill of an expert faced with the problem to provide additional enzymatic resistant inhibitors to modify said peptides by introducing D-aa residues.
5)The applicant has noticed in the description, page 13, lines 13-26, that it was unforseen that introduction of D-aa would result in (more) active compounds as klvff lacked any activity where its natural counterpart KLVFF was indeed active. However D1 shows analogs having all-D-aa substitution actually exhibiting the inhibiting activity. In this respect it is noted by the examiner that it apparently cannot be foreseen whether compounds of the present type would have advantageous properties compared to their natural counterparts different from an increased enzymatic stability.
6)Therefore, due to this non-obvious character of these effects, the present compounds are considered to be modifications for which only an inventive step can be acknowledged if it is demonstrated for at least a representative number of them that they exhibit unexpected advantageous properties not merely as a result of enzymatic stability.
At present only the compounds klvffa and kklvffa have been shown to have an unexpected high improved activity compared to the corresponding natural peptides. Hence at present the claims 1-7 and 9-36 are considered to lack an inventive step under Art.33(3) PCT.

For the assessment of the present claims 1-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.